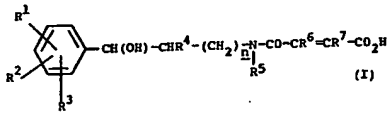
(12) UK Patent Application (19) GB (11) 2 011 389 A

(21) Application No 7848525
(22) Date of filing 14 Dec 1978
(23) Claims filed 14 Dec 1978
(30) Priority data
(31) 52422/77
(32) 16 Dec 1977
(31) 52421/77
(32) 16 Dec 1977
(33) United Kingdom (GB)
(43) Application published
11 Jul 1979
(51) INT CL²
C07C 103/60 A61K 31/19
(52) Domestic classification
C2C 200 220 226 227
22Y 282 29X 29Y 302
30Y 321 322 32Y 342 34Y
360 362 365 366 367 36Y
591 618 620 623 628
62X 633 650 652 658
662 682 778 779 802 80Y
KM LF LJ NN
(56) Documents cited
GB 1137696
(58) Field of search
C2C
(71) Applicant
Deutsche Gold-und Silber-Scheideanstalt vormals Roessler, 9 Weissfrauenstrasse, 6 Frankfurt Main 1, Germany
(72) Inventors
Karl Heinz Klingler,
Horst Traube,
Klaus Thiemer,
Fritz Stroman
(74) Agent
Elkington & Fife

(54) New Maleic Acid Semi-Amides, their Production and Use

(57) The invention relates to semi-amides of unsaturated aliphatic dicarboxylic acids corresponding to the general formula (I)



(I)

in which R^1, R^2 and R^3 which may be the same or different, each represent hydrogen, a halogen atom, a hydroxy group, a methyl group or a methoxy group or two of these radicals taken together represent a methylene dioxy group, R^4 is hydrogen or a methyl group, the radicals R^5, R^6 and R^7 independently of one another each represent hydrogen or a C_1—C_4-alkyl group and n=0 or 1, and their salts, excluding N-[2-(3-hydroxyphenyl)-2-hydroxyethyl]-maleic acid monoamide in the case of the free acids.

The semi-amides can be prepared by a process which comprises reacting a compound corresponding to the formula (II).

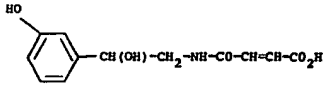
GB 2 011 389 A

SPECIFICATION

New Maleic Acid Semi-Amides, their Production and Use

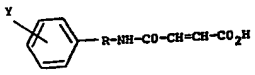
This invention relates to new maleic acid semi-amides, their production and their use in a process for the production of optically active bases.

N-[2-(3-Hydroxyphenyl)-2-hydroxyethyl]-maleic acid monoamide corresponding to the formula



is described in Example 6 of British Patent Specification No. 1,137,596. In this British Patent Specification, compounds such as these are said to be pharmacologically active in that they have an effect upon the circulation of blood and, in particular, a favourable effect at low blood pressure.

According to British Patent Specification No. 901,438, maleic acid monoamide derivatives corresponding to the general formula



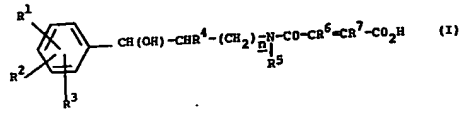
in which Y represents hydrogen, a halogen atom, a C_1—C_{10}-alkyl group or a C_1—C_{10}-alkoxy group and R is an ethylene or propylene group which may also be substituted inter alia by C_1—C_{10}-alkyl radicals and/or by a hydroxy group, counteract the secretion of penicillin in the organism. Some of these compounds are also said to be active against gout and to be capable of reducing the level of cholesterol in the blood stream.

In addition it is already known that (R) (S)-(1-phenylethyl)-amine, (R) (S)-2-amino-1-butanol and 1- (R) (S)-threo-1-(4-nitrophenyl)-2-amino-1,3-propane diol can be optically split by means of N-[(R)-(1-phenylethyl)]-or N-[(3)-1-phenylethyl)] succinic acid monoamide and that (R) (S)-1-phenyl-2-amino-propane can be optically split by means of N-[(R) or (S)-1-phenylethyl)]-phthalic acid monoamide (Helvetica Chimica Acta *52*, 329 (1969); US Patent No. 3,576,854).

It is also known that racemic norephedrine can be separated into the levorotatory and dextrorotatory form with optically active pantolactone (German Offenlegungsschrift No. 2,558,507).

In the known processes, however, the yields of the pure optically active forms are unsatisfactory. In many cases, the purity of the end products is also inadequate.

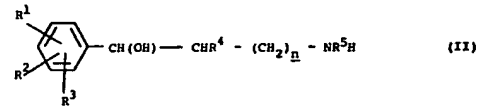
The present invention provides semi-amides of unsaturated aliphatic dicarboxylic acids corresponding to the general formula (I)



(I)

in which R^1, R^2 and R^3, which may be the same or different, each represent hydrogen, a halogen atom, a hydroxy group, a methyl group or a methoxy group or two of these radicals taken together respresent a methylene dioxy group, R^4 is hydrogen or a methyl group, the radicals R^5, R^6 and R^7 independently of one another each represent hydrogen or C_1—C_4-alkyl groups and n=0 or 1, and their salts, excluding N-[2-(3-hydroxyphenyl)-2-hydroxyethyl]-maleic acid monoamide in the case of the free acids.

The invention also provides a process for the production of compounds as defined above which comprises reacting a compound corresponding to the formula (II)



(II)

with a compound corresponding to the formula (III)

$$X—CO—CR^6=CR^7—CO_2H \qquad (III)$$

in which formulae, the radicals R^1 to R^7 are as defined above and any oxy groups present and also the carboxy group in the compound of formula (III) may be protected, and X is a halogen atom, a hydroxy group, a C_1—C_6-alkoxy group, a cyanomethoxy radical, a carboxymethoxy radical or an aryloxy group, or X forms a 5-membered acid anhydride ring with the free carboxy group.

Where the radicals R^1, R^2 or R^3 are halogen atoms, the halogen atoms in question are fluorine, chlorine or bromine, particularly chlorine. If the radicals R^5, R^6 or R^7 are alkyl groups, the alkyl groups in question are in particular methyl or ethyl groups.

The compounds according to the invention are pharmacodynamically active and have for example an antidepressive effect. In addition, the salts of the compounds according to the invention with phenyl alkylamines, particularly with norephedrine, *p*-hydroxy norephedrine and other norephedrine derivatives, show strikingly persistent effects upon the circulation (for example an increase in blood pressure and positive inotropic effects) together with an increase in renal circulation and diuretic activity.

Suitable salts are the physiologically compatible salts with metals, such as K, Na, Li, Mg, Ca or NH_3, or with amines or organic compounds containing one or more basic nitrogen atoms.

The following are examples of amines and basic organic compounds such as these:

a) primary, secondary or tertiary aliphatic alkylamines with alkyl radicals of 1 to 6 carbon atoms (triethylamine, diethylamine), C_2—C_6-alkylene diamines (ethylene diamine, propylene diamine), primary, secondary or tertiary alkanolamines with alkylene radicals of 2 to 6 carbon atoms (ethanolamine, diethanolamine, triethanolamine)

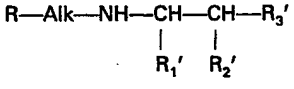
b) β-phenyl-C_1—C_4-alkylamines and β-phenyl-C_1—C_4-alkanolamines, in which the phenyl radical may be substituted, for example by C_1—C_5-alkyl groups, C_1—C_5-alkoxy groups, hydroxyl groups, hydroxymethyl groups or halogen atoms (F, Cl, Br) and whose amino group is also substituted by C_1—C_6-alkyl radicals, phenyl-C_1—C_4-alkyl radicals (which may also contain C_1—C_5-alkyl groups, C_1—C_5-alkoxy groups or hydroxyl groups in the phenyl nucleus) or C_1—C_5-alkyl or C_2—C_5-alkenyl radicals which are substituted by a heterocyclic radical (for example the thienyl or pyridyl radical) and, in addition, may even contain an oxo group or a hydroxy group in the alkyl or alkenyl moiety. Examples are norephedrine, amphetamine, *o*-, *p*-, or *m*-hydroxy norephedrine, 3,4-dihydroxy- or 3,5-dihydroxy norephedrine, β-(2-hydroxy-1-methylphenethylamino)-3-methoxy propiophenone

c) diphenyl-C_2—C_6-alkylamines of which the amino group is substituted by straight-chain or branched-chain C_1—C_5-alkyl radicals or phenyl-C_1—C_4-alkyl groups (for example the phenethyl group, phenyl isopropyl group). Examples are N-(1-methylphenethyl)-3,3-diphenyl propylamine

d) 1-aryloxy-2-propanolamines of which the amino group may be substituted by C_1—C_6-alkyl groups, phenyl-C_1—C_4-alkyl groups (for example the phenethyl group, phenyl isopropyl group) or heterocyclically substituted (for example by a pyridyl, thienyl or theophyllinyl or theobrominyl radical C_2—C_6-alkyl groups and whose aryl radical (which may also be substituted) is phenyl, naphthyl or tetrahydronaphthyl radical or a mono-, di or tri-cyclic hetero aromatic ring system (examples as given under f below). In particular, the aryl radical is an α-naphthyl radical, a phenyl radical, a o-allyloxy phenyl radical, a *p*-allyloxy phenyl radical, an indolyl-(4)-radical, a 2-methyl indolyl-(4)-radical or a 2,3-dimethyl indolyl-(4)-radical

e) alkaloids containing one or more basic nitrogen atoms such as, for example, atropine, hyoscyamine, scopolamine, codeine, ajmaline. sparteine

f) basically substituted xanthine derivatives, particularly theophylline and theobromine derivatives corresponding to the general formula



in which T is a dialkyl xanthinyl radical, Alk is a straight-chain or branched-chain C_2—C_6-alkylene group, R_1' is hydrogen or a C_1—C_4-alkyl group, R_2' is hydrogen or a hydroxy group and R_3' is a phenyl radical optionally substituted one or more times by hydroxy groups (particularly once or twice), C_1—C_5-alkyl groups, C_1—C_5-alkoxy groups, hydroxymethyl groups or by the methylene dioxy group or an aryloxy methyl radical, the aryl radical being the naphthyl radical, the tetrahydronaphthyl radical or a mono-, di or tri-cyclic heteroaromatic ring system which may even be substituted once to three times by lower alkyl, alkoxy, alkenyl or alkenyloxy groups. Examples of the heteroaromatic ring system are indole, isoindole, benzimidazole, quinoline, dihydroquinoline, tetrahydroquinoline, isoquinoline, pyrazole, thiazole; methyl indole, methyl isoindole, methyl benzimidazole, methyl quinoline, methyl dihydroquinoline, methyl tetrahydroquinoline, methyl isoquinoline, methyl pyrazole, methyl thiazole, dimethyl indole, dimethyl quinoline, dimethyl isoquinoline, dimethyl benzimidazole (in the case of the bicyclic radicals, the methyl group or groups is/are preferably situated in the ring which contains the hetero atom).

Salts in which the basic component corresponds to formula (II) and the symbols R^1 to R^5 and *n* are as defined above, have particularly favourable effects. Examples for this are norephedrine, *n*-hydroxy norephedrine, 3,4-dihydroxy norephedrine, noradrenalin, ephedrine, 3,4-dihydroxy ephedrine, *m*-hydroxy norephedrine.

The compounds according to the invention are produced by reacting a compound corresponding to formula (II) with a compound corresponding to formula (III) in the presence or absence of solvents at a temperature of from 0 to 200°C and particularly at a temperature of from 15 to 150°C. Suitable solvents or suspending agents are aromatic hydrocarbons, such as benzene, toluene, xylene, aliphatic halogenated hydrocarbons such as chloroform, methylene chloride, acyclic or cyclic ethers such as tetrahydrofuran, dioxane, diethyl ether, alcohols such as ethanol, isopropanol, butanol, diisopropyl ether, pyridine, tetramethyl urea, dimethyl formamide, dimethyl sulphoxide, N-methyl pyrrolidone.

In some cases, it is of advantage to use reaction component (III) in excess (particularly where X is an alkoxy group). It may be favourable to add condensation agents, such as dicyclohexyl carbodiamide, tetraethyl pyrophosphite, 5(3'-sulphophenyl)-ethyl isooxazole, sulphurous acid-bis-alkylamides (for example $SO[N\,CH_3)_2]_2$) or N,N'-carbonyl dilmidazole (where X=OH), or basic substances (tertiary amines, alkali metal carbonates, alkali metal hydrogen carbonates, alkali metal acetates, alkaline earth metal carbonates, alkali metal hydroxides, etc.). The amine component (II) may even be used in the form of an acid addition salt. In this case, the addition of acid-binding bases is generally necessary. Where X in the compound of formula (III) is a halogen atom, the halogen atom in question is Cl, Br or I, preferably Cl or Br. Where X in the compound of formula (III) is an aryloxy group, the aryloxy group in question is for example a phenoxy group, in which case the phenyl radical may even be substituted by lower alkyl radicals, lower alkoxy radicals, halogen atoms (Cl, F, Br), nitro groups or cyano groups.

Any hydroxy groups present in the starting compounds of formula (II), particularly phenolic hydroxy groups (where R^1, R^2 and/or R^3 represent

OH) and also the carboxy group in the compound of formula (III) may contain known protective groups of the usual type. The protective groups in question are radicals which may readily be split off by hydrolysis and which may even be split off during the reaction. Where protective groups such as these are not split off during the reaction on which the process is based, they are split off after the reaction. In many cases, the starting compounds already contain protective groups of the type in question from their production.

These protective groups are for example acyl groups which can readily be split off by solvolysis. The protective groups which can be eliminated by solvolysis are split off for example by hydrolysis with dilute acids or by means of basic substances (potash, soda, aqueous alkali solutions, alcoholic alkali solutions, NH_3) at a temperature of from 10 to 150°C and particularly at a temperature of from 20 to 100°C.

Examples of radicals which can be split off by hydrolysis are the trifluoroacetyl radical, the phthalyl radical, the trityl radical, the *p*-toluene sulphonyl radical and the like, and also lower alkanoyl radicals, such as the acetyl radical, the formyl radical, the tert.-butyl carboxy radical and the like.

The salts are produced by combining the acids of formula (I) with the corresponding amines in one of the usual solvents (lower aliphatic alcohols, lower aliphatic ketones, esters of lower aliphatic acids with lower alcohols) at a temperature of from 15 to 100°C and particularly at a temperature of from 20 to 60°C.

In general, the components are used in equivalent quantities. In the case of the metal salts, the corresponding metal hydroxide or metal carbonate for example is used as the basic component.

The salts of the end products may be converted back into the compounds of formula (I) in known manner, for example with fairly strong acids (for example inorganic mineral acids) or ion exchangers.

In the context of the invention, the compounds of general formula (I) also include the possible stereoisomeric and optically active compounds and mixtures thereof, particularly the racemates. Mixtures of disastereoisomers can be separated in known manner, for example by fractional crystallisation. Optically active compounds may be obtained by the usual methods, for example by recrystallising salts of the racemic acids of formula (I) with optically active bases or optionally by using optically active starting products at the synthesis stage. The organic basic compounds which may be used for salt formation may also exist as pure optically active forms, as racemates or as disastereomers.

The compounds according to the invention are suitable for the preparation of pharmaceutical compositions and preparations. The pharmaceutical compositions or medicaments contain as active principle one or more of the compounds according to the invention, optionally in admixture with other pharmacologically or pharmaceutically active substances. The medicaments are preapred in known manner with the usual pharmaceutical additives and other conventional excipients and diluents.

Examples of excipients and additives of this kind are the substances recommended and specified in the following literature references as additives for pharmacy, cosmetics and related fields: Ullmanns Encyklopadie der technischen Chemie, Vol. 4 (1953), pages 1 to 39; Journal of Pharmaceutical Sciences, Vol. 52 (1963), pages 918 *et seq*, H.v.Czetsch-Lindenwald, Hilfsstoffe fur Pharmazie und angrenzende Gebiete; Pharm. Ind., No. 2, 1961, pages 72 *et seq;* Dr. H.P. Fiedler, Lexikon der Hilfsstoffe fur Pharmazie, Kosmetik und agrenzende Gebiete Cantor KG. Aulendorf (Wurtt.) 1971.

Examples include gelatin, natural sugars, such as cane sugar or lactos, lecithin, pectin, starch (for example corn starch), alginic acid, tylose, talcum, lycopodium, silica (for example colloidal silica), cellulose, cellulose derivatives (for example cellulose ethers in which the cellulose hydroxy groups are partly etherified with lower saturated aliphatic alcohols and/or lower saturated aliphatic hydroxy alcohols, for example methyl hydroxy propyl cellulose), stearates, magnesium and calcium salts of fatty acids with 12 to 22 carbon atoms, especially the saturated fatty acids (for example stearates), emulsifiers, oils and fats, especially vegetable oils and fats (for example peanut oil, castor oil, olive, sesame oil, cottonseed oil, corn oil, wheat germ oil, sunflower seed oil, cod liver oil, mono-, di, and tri-glycerides of saturated fatty acids $C_{12}H_{24}O_2$ to $C_{18}H_{36}O_2$ and mixtures thereof), pharmaceutically compatible monohydric or polyhdric alcohols and polyglycols, such as polyethylene glycols and derivatives thereof, esters of aliphatic saturated or unsaturated fatty acids (2 to 22 carbon atoms, especially 10 to 18 carbon atoms) with monohydric aliphatic alcohols (1 to 20 carbon atoms) or polyhydric alcohols, such as glycols, glycerol, diethylene glycol, pentaerythritol, sorbitol, mannitol and so on, which optionally may even be etherified, benzyl benzoate, dioxolanes, glycerol, formals, tetrahydrofurfuryl alcohol, polyglycol ethers with C_1—C_{12}-alcohols, dimethyl acetamide, lactamides, lactates, ethyl carbonates, silicones (especially medium-viscosity dimethyl polysiloxanes), magnesium carbonate and the like.

Solutions can be prepared, for example, with water or physiologically compatible organic solvents, such as for example, ethanol, 1,2-propylene glycol, polyglycols and derivatives thereof, dimethyl sulphoxide, fatty alcohols, triglycerides, partial esters of glycerol, paraffins and the like.

Conventional solution promoters and emulsifiers may be used in the preparation of the compositions. Examples of solution promoters and emulsifiers include polyvinyl pyrrolidone, sorbitan fatty acid esters, such as sorbitan

trioleate, lecithin, acacia, tragacanth, polyoxyethylated sorbitan monooleate, polyoxyethylated fats, polyoxyethylated oleotriglycerides, linolised oleotriglycerides, polyethylene oxide condensation products of fatty alcohols, alkyl phenols or fatty acids, Polyoxyethylated in this context means that the substances in question contain polyoxyethylene chains with a degree of polymerisation of generally from 2 to 40, more particularly from 10 to 20.

Polyoxyethylated substances of this kind can be obtained for example by reacting compounds containing hydroxy groups (for example monoglycerides or diglycerides or unsaturated compounds, such as for example those containing oleic acid residues) with ethylene oxide (for example 40 moles of ethylene oxide per mole of glyceride).

Examples of oleotriglycerides include olive oil, peanut oil, castor oil, sesame oil, cottonseed oil, corn oil (see also Dr. H.P. Fiedler "Lexikon der Hilfsstoffe fur Pharmazie, Kosmetik und angrenzende Gebiete" 1971, pages 191 to 195).

In addition, it is possible to add preservatives, stabilisers, buffers, for example calcium hydrogen phosphate, colloidal aluminium hydroxide, flavour correctants, anti-oxidants and complex formers (for example ethylene diaminotetraacetic acid) and the like. To stabilise the active-principle molecule, the pH may have to be adjusted to a range of from about 3 to 7 with physiologically compatible acids or buffers. A neutral to weakly acid (up to pH 5) pH-value is generally preferred.

Examples of suitable antioxidants include sodium meta-bisulphite, ascorbic acid, gallic acid, gallic acid, alkyl esters, butyl hydroxy anisole, nordihydroguariaretic acid, tocopherols and tocopherols plus synergists (substances which bind heavy metals by complex formation, for example lecithin, ascorbic acid, phosphoric acid). Addition of the synergists greatly increases the antioxygenic effect of the tocopherols.

Examples of preservatives include sorbic acid, *p*-hydroxy benzoic acid esters (for example lower alkyl esters), benzoic acid, sodium benzoate, trichloro-isobutyl alcohyl, phenol, cresol, benzethonium chloride and formalin derivatives.

The compounds according to the invention are pharmacologically and galenically handled by the usual standard methods. For example, active principle(s) and additives or excipients are thoroughly admixed by stirring or homogenisation (for example in colloid mills, ball mills), generally at temperatures of from 20 to 80°C and preferably at temperatures of from 20 to 50°C.

The active principles or medicaments may be applied to the skin or mucosa or into the interior of the body, for example orally, enterally, pulmonarily, rectally, nasally, vaginally, lingually, intravenously, intra-arterially, intracardially, intramuscularly, intraperitoneally, intracutaneously, subcutaneously.

In particular, the addition of other active medicaments is also possible.

The compounds according to the invention have a circulation-stimulating effect and, in particular, a blood-pressure-increasing effect in aneasthetised dogs, as determined by electronic measurement of blood pressure, contractility and cardiac output.

Blood pressure was directly measured in the usual way (sanguineously) by electronic manometers (Stathan). Contractility (dp/dt_{max}) was determined from the pressure of the left ventricle (Schaper et al's method, Arch. Kreislaufforch. *46*, 27, 1965). Cardiac output was determined by the cold dilution method (according to Hamilton, W.F. et al, Am. J. Physiol. *99*, 543, 1932) by means of a fixed-program analog computer (H. Slama and J. Piiper's method: Kreislaufforschung *53*, 322 (1964).

In the above-mentioned test method for example, a dose of 1 mg per kg of dog body weight increases the mean arterial pressure by around 20% and cardiac output by around 100%. Contractility (pressure increase rate) is increased by around 70%.

The circulation-stimulating effect is comparable with the effect of the known medicament norephedrine.

The lowest dose by which blood pressure is increased in the above-mentioned animal test is for example 0.3 mg/kg (oral) or 0.1 mg/kg (intravenous).

The general dosage range for the blood-pressure-increasing effect in the above-mentioned animal test is for example from 1 to 10 mg/kg, more particularly 3 mg/kg (oral), or from 0.1 to 1 mg/kg, more particularly 0.3 mg/kg (intravenous).

Indications for which the compounds according to the invention may be considered include heart circulation failure, shock-induced disturbances, hypotonia, orthostatic disturbances, collapse.

The pharmaceutical preparations generally contain from 1 to 50 mg of the active component(s) according to the invention.

The active component(s) according to the invention may be made up in the form of tablets, capsules, pills, dragees, suppositories, aerosols or liquids. Examples of suitable liquid formulations are oily or alcoholic and aqueous solutions and also suspensions and emulsions. Preferred formulations are tablets containing from 1 to 50 mg of active substance or solutions containing from 0.5 to 5% of active substance.

The active components according to the invention may be used in individual doses of for example

a) from 5 to 40 mg in the case of oral formulations,

b) from 1 to 20 mg in the case of parenteral formulations (for example intravenous, intramuscular),

c) from 1 to 5 mg in the case of formulations for inhalation (solutions or aerosols),

d) from 5 to 30 mg in the case of formulations for rectal or vaginal application,

(these doses being based on the free base in each case).

For example, 1 to 3 tablets containing from 5 to 40 mg of active substance may be prescribed three times daily or, for example in the case of intravenous injection, one 1 to 10 ml. ampoule containing from 1 to 20 mg of active substance may be prescribed 1 to 6 times daily. In the case of oral administration, the minimum daily dose is for example 10 mg, whilst the maximum daily dose should not exceed 120 mg.

In the treatment of dogs and cats, the individual oral dose is generally between about 1 and 20 mg/kg body weight; the individual parenteral dose is between about 0.1 and 3 mg/kg body weight.

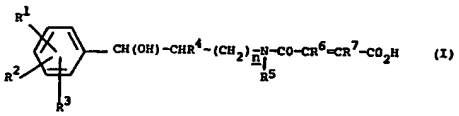
In the treatment of horses and cattle, the individual oral dose is generally between about 1 and 20 mg/kg and the individual parenteral dose between about 0.1 and 3 mg/kg body weight.

The medicaments may be used in human medicine, verterinary medicine and agricultural medicine either individually or in admixture with other pharmacologically active substances.

The toxicity of the compounds accordingly, expressed as LD_{50} on the mouse by month, is generally above 500 mg/kg.

In addition, the free acids of general formula (I) represent valuable racemate splitting resolution reagents for racemic bases and are therefore of particular importance for the production of optically active pharmaceutical active principles.

The present invention thus also provides a process for the production of an optically active base which comprises reacting a racemic base with an optically active semiamide of an unsaturated aliphatic dicarboxylic acid corresponding to the general formula (I)



(I)

in which

R^1, R^2 and R^3 which may be the same or different, each represent hydrogen, a halogen atom, a hydroxy group, a methyl group or a methoxy group or two of these radicals taken together represent a methylene dioxy group, R^4 is hydrogen or a methyl group, the radicals R^5, R^6 and R^7 independently of one another each represent hydrogen or a C_1—C_4-alkyl group and n=0 or 1, and optionally after fractionation at least one optically uniform salt fraction is split up into the corresponding optically active base and the semi-amide used.

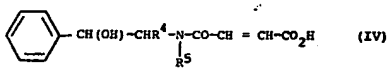
The process according to the invention enables optically active physiologically active amines to be readily obtained in the requisite purity.

For the racemate splitting resolution reaction according to the invention, equivalent or non-equivalent quantities of amido-acid (0.4 to 1.2 moles, preferably 0.5 to 1.0 mole of amido acid per mole of base) and base may be reacted with one another in a solvent at a temperature of from 0 to 100°C, for example at a temperature of from 10 to 40°C and preferably at a temperature of from 15 to 30°C. The reaction may be carried out with or without stirring. Gradual cooling during the crystallisation process may be advisable. Inoculation with the required diastereoisomeric salt produced beforehand from pure components may be recommended. As in other resolution processes, the quantities of solvent or solvent mixtures used are variable within wide limits. Suitable solvents are, for example, alcohols such as methanol, ethanol, isopropanol, butanol; ketones such as acetone, methylethyl ketone, methyl isobutyl ketone; esters such as ethylacetate and butylacetate; amides such as dimethyl formamide and dimethyl acetamide; ethers such as diethyl ether and dioxane; water, particularly in admixture with organic solvents.

In general, the quantity of solvent used amounts to between 2 and 20 times and preferably to between about 3 and 8 times the total quantity of acid and base used.

For the reaction with the amino acids, the amines may even be used in the form of corresponding salts with acids, preferably weak acids (for example acetates). In this case, the amido acid may even be used in the form of a metal salt (for example an alkali metal salt).

Semi-amides corresponding to the general formula (IV)



(IV)

in which R^4 is hydrogen or a methyl group and R^5 is hydrogen or a C_1—C_4-alkyl group, for example a methyl group, or in which R^4 and R^5 are both hydrogen, are particularly suitable for the resolution process according to the invention. It is preferred to use semiamides of formula (IV) in which R^4 is a methyl group and R^5 is a hydrogen, for example the maleic acid semi amide of (+)-pseudonorephedrine or of (—)-pseudonorephedrine.

Where the amine component of the semi-amide of formula (I) or formula (IV) contains several asymmetrical centres, as for example in the case of norephedrine and norephedrine derivatives which are substituted in the phenyl nucleus, it is frequently of advantage to alter the configuration of one of the asymmetrical centres of the basic component in known manner before the semi-amides are produced. This may be done in particular by the rearrangement of (+)-norephedrine into (—)-ψ-norephedrine ((—)-pseudonorephedrine) or by the rearangement of (—)-norephedrine into (+)-ψ-norephedrine ((+)-pseudonorephedrine). The same applies to (+)- or (—)-norephedrine which is substituted in the phenyl nucleus by the radicals R^1, R^2 and R^3 according to formula (I). These pseudo forms are particularly suitable for, the resolution reaction.

The above-mentioned rearrangement of

optically active norephedrine into the corresponding oppositely rotating pseudonorephedrine is described in the literature. The OH-group of the norephedrine is replaced by chlorine using $SOCl_2$ or HCl, followed by hydrolysis in the reaction mixture by boiling with H_2O to reform the OH-group (Walden's reversal). It is even possible to acylate (for example acetylate) the amino group for protection before chlorination and subsequently to split off the acyl group in the usual way by hydrolysis or hydrogenolysis. Exactly the same procedure is adopted for the norephedrine derivatives which are substituted in the phenyl nucleus by the radicals R^1, R^2, and R^3.

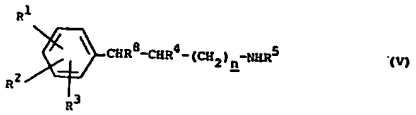
In the resolution process according to the invention, one of the pure diastereomeric forms is immediately precipitated after the reaction of the semi-amide (I) with the base, whilst the other remains in solution. However, if in one or the other case the diastereomeric form precipitating is rendered relatively impure by the other form, the one form is purified in the usual way by fractional crystallisation.

The diastereomers obtained by the process according to the invention may readily be split up using alkali (for example alkali metal hydroxides, such as sodium or potassium hydroxide), ammonia or a mineral acid, such as hydrochloric or sulphuric acid. The substantially insoluble diastereomer is treated for example with the alkali (preferably NH_3 or NaOH) and, if the base does not precipitate, it is extracted with a solvent which is incompatible or immiscible with water, such as chloroform, methylene chloride, benzene or ether, in which case the optically active form may be isolated in high purity from the organic phase. The mother liquor from which the substantially insoluble diastereomer was separated off is generally distilled off and the residue is taken up in a solvent in which the residual (±)-base separates in insoluble form (for example aromatic hydrocarbons, such as toluene, xylene, benzene). After a few hours, the (±)-base is separated off and the filtrate concentrated by evaporation, leaving behind the other antipode of the base.

The aqueous phase, from which the optically active base was extracted, is then acidified with a mineral acid (HCl, H_2SO_4), as a result of which the amido acid precipitates. The amido acids thus recovered may be reused for the resolution reaction, generally without further purification.

If the salts obtained during the resolution reaction are decomposed with acids (mineral acids) such as (HCl, H_2SO_4), it is the amido acid which precipitates first. The filtrate is alkalised either directly or after concentration and the optically active base is extracted by a solvent (lower aliphatic halogenated hydrocarbons, such as chloroform, or lower aliphatic dialkyl ethers, such as diethyl ether.

Suitable racemic bases which may be split by the process are, in particular, amines corresponding to the formula (V)

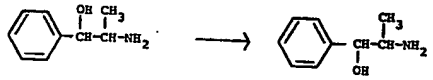


(V)

in which R^1, R^2 and R^3, which may the same or different each represent hydrogen, a halogen atom, a hydroxy group, a methyl group or a methoxy group or two of these radicals together represent a methylene dioxy group, R^4 is hydrogen or a methyl group, R^5 is hydrogen or a C_1—C_4-alkyl group, R^8 is hydrogen of a hydroxy group and n=0 or 1. It is preferred to use amines of formula (V) in which R^1, R^2, R^3, R^5 represent hydrogen, R^8 is hydrogen or, in particular, a hydroxy group R^4 is hydrogen or a methyl group and n=0. It is possible by preliminary tests to determine which amido acid is most suitable for which base in any particular case.

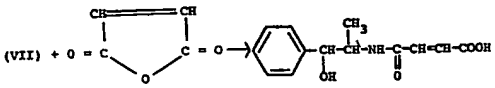
One major advance of the process according to the invention lies in the fact that the antipode obtained as secondary product during the resolution reaction, which is pharmaceutically unuseable and which cannot even be converted back into the original racemate by racemisation, can be converted into the amido acid of formula (I). In this way, new racemates can be split with this otherwise worthless secondary product.

The advantages of the resolution process according to the invention are explained in the following with reference to the technically important resolution of (±)-norephedrine (NE). The dextrorotatory antipode (+)-norephedrine ((+)-NE; formula (VI), which is pharmaceutically unuseable, is rearranged in known manner (see above into the (—)-ψ-norephedrine (formula (VII), (—)-ψ-NE).



(VI) (+)-NE (VII) (-)-Ψ-NE

The corresponding amido acid (formula (VIII), (+)-ψ-NEMA) is obtained therefrom in a high yield by reaction with maleic acid anhydride:



(VIII), (+)-Ψ-NEMA

The substantially insoluble (—)-NE-salt of the (+)-ψ-NEMA precipitates simply by stirring this acid with (±)-norephedrine in a solvent. Acid or alkaline decomposition of the salt obtained gives (—)-norephedrine and the unchanged (+)-ψ-NEMA. The small losses of (+)-ψ-NEMA readily be compensated by the reaction sequence described above starting out from the (+)-norephedrine which also accumulates from mother liquors during the racemate splitting reaction.

By contrast, where succinic acid or phthalic acid derivatives analogous to formula (VIII) are used, the racemate separation of (±)-norephedrine is highly unsatisfactory. The yields and crystallisability of the diastereomeric salts are poor, in addition to which the undesirable (+)-NE-form initially precipitates as a substantially insoluble component during the salt forming reaction. It is surprising that, through the changeover from an unsaturated or an aromatic dicarboxylic acid to an unsaturated dicarboxylic acid, the amido acids produced therefrom and from the worthless optical antipodes of an amine of formula (III) form diastereomeric salts of optically active bases which show the optimal solubility and crystallisation properties required for a resolution reaction. In addition, it is surprising that, in the case of salts of the amido acids of which the corresponding bases contain more than one asymmetrical centre, the differences in solubility can be further increased by reversing the configuration on one of these centres (for example converting norephedrine into the corresponding pseudoform) before production of the amido acid.

Another advantage lies in the simple recovery of the amido acid used after the racemate splitting reaction.

The invention is illustrated by the following Examples in which Examples 1 to 6 illustrate the production of the compounds according to the invention, Examples 7 and 8 illustrate pharmaceutical compositions containing them and Examples 9 to 14 illustrate the resolution process according to the invention.

Example 1
(+)-ψ-N-(1-methyl-2-phenyl-2-hydroxyethyl)-maleic acid monoamide (abbreviation: (+)-ψ-NEMA)

165.4 g of maleic acid anhydride are dissolved in 1250 ml of warm toluene. A solution heated to 50°C of 255 g of (−)-ψ-norephedrine in 1250 ml of toluene is quickly added dropwise with stirring to the resulting solution, followed by stirring for 1 hour at an internal temperature of 80°C. After cooling to room temperature, the amido acid which has crystallised out is filtered off under suction and dried *in vacuo* at 60°C.

Yield: 419.9 g (=99.9% of the theoretical).

After recrystallation, the reaction product melts at 152 to 155°C.

$[\alpha]_D^{20}$ (2.5% in 96% ethanol: +17.64°.

(−)-Norephedrine salt

25 g of (−)-norephedrine and 41.2 g of (+)-ψ-NEMA are dissolved in 200 ml of hot acetone. The salt crystallises out on cooling.

Yield: 64.5 g=97.6% of the theoretical.

M.p.: 149—151°C.

$[\alpha]_D^{20}$ (2.5% in ethanol): −64.4°.

Example 2
(−)-N-(1-methyl-2-phenyl-2-hydroxyethyl)-maleic acid monoamide (abbreviation: (−)-NEMA)

16.3 g of maleic acid anhydride are dissolved in 300 ml of toluene. A solution heated to 50°C of 25.0 g of (−) norephedrine in 50 ml of toluene is added dropwise with stirring to the resulting solution. After stirring for 1 hour at the above-mentioned temperature, the product is allowed to cool and is then filtered off under suction. It may be purified by recrystallisation from ethylacetate.

Yield: 32.6 g=79% of the theoretical.

M.P.: 155—158°C

$[\alpha]_D^{20}$ (5% in ethanol); −7.69°.

(−)-Ephedrine salt.

20.6 g of (−)-ephedrine and 31 g of (−)-NEMA are dissolved in 155 ml of acetone. Dry ether is then added until the solution remains permanently clouded. After standing for several days at room temperature, the product is filtered off under suction and dried *in vacuo*.

Yield: 37.5 g=83% of the theoretical; m.p. 118—122°C.

$[\alpha]_D^{20}$ (1% in 96% ethanol): −39.5°.

(−)-Norephedrine salt.

25 g of (−)-norephedrine and 41.2 g of (−)-NEMA are dissolved in 200 ml of hot acetone. After cooling, the crystalline salt is filtered off under suction.

Yield; 56.3 g=85% of the theoretical.

M.p. 142—144°C.

$[\alpha]_D^{20}$ (1% in ethanol): +7.39°.

(−)-ψ-Norephedrine salt

34.5 g of (−)-ψ-norephedrine and 57 g of (−) NEMA are dissolved in 460 ml of hot ethylacetate. After cooling to room temperature, the product is filtered off under suction and dried.

Yield: 90.5 g=98.4% of the theoretical.

M.p. 153—155°C

$[\alpha]_D^{20}$ (1% in ethanol): 7.70°.

(−)-*p*-hydroxy norephedrine salt.

10 g of (−)-*p*-hydroxy norephedrine and 14.9 g of (−)-NEMA are stirred for 2 hours at 125 ml of isopropanol. After standing for 15 hours at 20°C, the product is filtered off under suction and dried *in vacuo* at 50°C.

Yield: 23.5 g=94.4% of the theoretical.

M.p. 162—164°C

$[\alpha]_D^{20}$ (1% in ethanol): +3.8°.

This salt may also be obtained from racemic *p*-hydroxy norephedrine using the racemate-splitting properties of the maleic acid amide according to Example 2:

A mixture of 100 g of (+)-*p*-hydroxy norephedrine, 149 g of (−)-NEMA and 1.25 litres of absolute ethyl alcohol is stirred for 8 hours at 20°C and left standing for another 16 hours. The (−)-NEMA salt of the (−)-*p*-hydroxy norephedrine which crystallises out is filtered off under suction and thoroughly boiled with 550 ml of isopropanol for purification. After cooling, the product is filtered under suction and dried *in vacuo* at 60°C.

Yield: 94.3 g=75.7% of the theoretical.
M.p.: 163—165°.
$[\alpha]_D^{20}$ (1% in absolute ethanol): +4.1°.

Example 3
(—)-ψ-N-(1-methyl-2-phenyl-2-hydroxyethyl)-methyl maleic acid monoamide

A mixture of 14 g of citraconic acid anhydride and 18.9 g of (—)-ψ-norephedrine is stirred for 5 hours at 40 to 50°C in 180 ml of dimethyl formamide. After cooling, another 18.9 g of (—)-ψ-norephedrine are added with stirring, the reaction solution obtained is filtered and the solvent is distilled off *in vacuo*. The residual salt is dissolved in cold water and, after acidification with hydrochloric acid, is stirred for 1 hour. The product is then filtered off under suction, washed with water and dried *in vacuo* at 60°C.
M.p.: 137—140°C
$[\alpha]_D^{20}$ (2.5% in 96% ethanol: —1.6°.

Example 4
(+)-N-(1-methyl-2-phenyl-2-hydroxyethyl)-maleic acid monoamide (abbreviation: (+)-NEMA)

32.6 g of maleic acid anhydride are dissolved in 600 ml of toluene, followed by the dropwise addition to the resulting solution with stirring of a solution, heated to 50°C, of 50.0 g of (+)-norephedrine in 100 ml of toluene. The mixture is then stirred for 30 minutes at the above-mentioned temperature. The product is then left to cool, filtered under section, dried and recrystallised from ethylacetate.
Yield 63.5 g=77.0% of the theoretical.
M.p.: 154—156°C.
$[\alpha]_D^{20}$ (5% in ethanol): +7.8°.

(+)-Norephedrine salt

50 g of (+)-norephedrine and 82.4 g of (+)-NEMA are dissolved in 400 ml of hot isopropanol. The solution is filtered, followed by gradual cooling to 5°C. The salt which has crystallised out is filtered under suction and dried *in vacuo* at 60°C.
Yield: 118.3 g=89.5% of the theoretical.
M.p.: 141—143°C.
$[\alpha]_D^{20}$ (1% in ethanol): —7.40°.

(+)-ψ-Norephedrine salt

34.5 g of (+)-ψ-norephedrine and 57 g of (+)-NEMA are dissolved in 460 ml of hot ethylacetate. After cooling to room temperature, the product is filtered under suction and dried.
Yield: 90.5 g=98.4% of the theoretical.
M.p.: 153—156°C.
$[\alpha]_D^{20}$ (1% in ethanol): —7.70°.

Example 5
(—)-N-(1-methyl-2-*p*-hydroxyphenyl-2-hydroxyethyl)-maleic acid monoamide (abbreviation: (—)-*p*-hydroxy NEMA)

50 g of (—)-*p*-hydroxy norephedrine are stirred with 29.3 g of maleic acid anhydride in 100 ml of dimethyl formamide. After the weakly exothermic reaction has abated, the mixture is heated to 80°C and left standing at that temperature for 1 hour. Following the addition of 100 ml of water, the reaction mixture is stirred for 1 hour, filtered under suction on the following day and dried *in vacuo*.
Yield: 76.1 g=96% of the theoretical.
M.p.: 146—148°C.
For purification, the product is subsequently stirred with cold isopropanol, filtered under suction and dried.
M.p.: 150—152°C.
$[\alpha]_D^{20}$ (2% in 96% ethanol): —13.05°.

Example 6
(+)-N-(1-methyl-2-*p*-hydroxyphenyl-2-hydroxyethyl)-maleic acid monoamide (abbreviation: (+)-*p*-hydroxy NEMA)

100 g of (+)-*p*-hydroxy norephedrine are stirred with 60.8 g of maleic acid anhydride in 150 ml of dimethyl formamide. After a weakly exothermic reaction has abated, the mixture is heated to 80°C and left standing at that temperature for 1 hour. Following the addition of 100 ml of water, the mixture is stirred for 1 hour, filtered under suction on the following day and dried *in vacuo*.
Yield: 120 g of pure (+)-*p*-hydroxy-NEMA.
M.p.: 151—153°C.
$[\alpha]_D^{20}$ (2% in 96% ethanol): +12.9°.
Instead of dimethyl formamide, isopropanol may also be used as solvent.

Example 7
Example for Tablets

25 g of (—)-norephedrine salt of (—)-NEMA are mixed with 25 g of colloidal silica, 5 g of corn starch and 60 g of lactose. The powder is granulated with a solution of 2.5 g of methyl oxypropyl cellulose in approximately 80 ml of 30% ethanol, the dried granulate is mixed with 10.5 g of corn starch, 9 g of talcum, 62.5 g of microcrystalline cellulose and 0.5 g of magnesium stearate and the resulting mixture pressed in known manner to form tablets. One tablet weighing 200 mg contains 25 mg of active principle.

Example 8
Example for an Injection Solution

10 mg of (—)-*p*-hydroxy norephedrine salt of (—)-NEMA are dissolved in 200 mg of propylene glycol and the solution is made up with twice-distilled water to 2.0 ml. After filtration through a sterile filter, the solution is introduced into ampoules under asceptic conditions.

Example 9
(—)-Norephedrine

250 g of (±)-norephedrine and 206 g of (+)-ψ-N-(1-methyl-2-phenyl-2-hydroxyethyl)-maleic acid monoamide (abbreviation: (+)-ψ-NEMA) are stirred for 6 hours in 2.28 litres of methylethyl

ketone at an internal temperature of 10 to 12°C. The precipitated (+)-ψ-NEMA salt of the (—)-norephedrine is then filtered off under suction. After washing with acetone, it is dried *in vacuo* at 60°C.

Yield: 309.8 g =93.6% of the theoretical;
m.p. 148—150°C.
$[\alpha]_D^{20}$ (2.5% in 96% ethanol): —63.4°.

300 g of this salt are suspended in 250 ml of water, followed by the addition of 68 ml of 45 % sodium hydroxide solution. The product is extracted by shaking once with 450 ml of chloroform and six times with 150 ml of chloroform. The combined chloroform extracts are dried with potassium carbonate and the solvent is distilled off under reduced pressure. The residue is dissolved in 450 ml of toluene, the resulting solution is inoculated after cooling with (±)-norephedrine base and is then placed for 12 hours in water at 10°C, a small quantity of unchanged (±)-norphedrine precipitating (10.5 g after drying). The toluene filtrate is distilled off *in vacuo*. The residue which crystallises on cooling consists of pure (—)-norephedrine.

Yield: 98.9 g=87% of the theoretical;
m.p. 49—51°C.
$[\alpha]_D^{20}$ (5% in ethanol): —13.84°.

Recovery of the (+)-ψ-NEMA

750 ml of water and 204 ml of concentrated hydrochloric acid are added while cooling to the aqueous phase separated off during extraction of the (—)-norephedrine by shaking. After cooling for a few hours with water, the product is filtered off under suction, washed with water and dried *in vacuo* at 60°C.

Yield: 176 g=94% of theoretical;
m.p. 149—151°C.
$[\alpha]_D^{20}$ (2.5% in 96% ethanol): +17.2°.

(+)-Norephedrine

The acetone filtrate obtained during resolution of the (±)-norephedrine is acidified while cooling with concentrated sulphuric acid. The crude (+)-norephedrine sulphate precipitated is filtered off under suction and dried at 80°C. Gross yield: 168 g.

156.5 g of this sulphate are stirred into 313 ml of water, alkalised with 80 ml of 45% sodium hydroxide solution and extracted by shaking six times with chloroform. After drying and distilling off the combined extracts, the residue is dissolved in 470 ml of toluene, inoculated with (±)-norephedrine and left standing for 12 hours at 10°C. The (±)-norephedrine base precipitated is filtered off under suction (24.6 g) and the toluene is distilled off under reduced pressure.

Yield: 95.2 g=80.5% of the theoretical;
m.p. 48—50°C.
$[\alpha]_D^{20}$ (5% in ethanol): +13.55°.

Example 10
(—)-Norephedrine

10 g of (±)-norephedrine and 16.5 g of (+)-N-(1-methyl-2-phenyl-2-hydroxyethyl)-maleic acid monoamide (abbreviation: (+)-NEMA) are stirred for 6 hours at 50°C in 160 ml of methyl isobutyl ketone. After standing overnight at 50°C, the product is filtered off under suction, washed with methyl isobutyl ketone and dried *in vacuo* at 60°C. Yield of (—)-norephedrine-(+)-NEMA-salt: 9.7 g=73% of the theoretical; m.p. 156—166°C.

The resulting 9.7 g of the (—)-norephedrine salt are suspended in 75 ml of water, 2.2 ml of concentrated hydrochloric acid are added, followed by stirring for 15 minutes. The (+)-NEMA precipitated is filtered off under suction, washed with water and dried at 60°C.

Yield: 5.7 g=94.6% of the theoretical.

To isolate the (—)-norephedrine, the aqueous filtrate is concentrated by evaporation *in vacuo*, the residue is stirred with acetone and the crude hydrochloride is filtered off under suction. Recrystallisation from isopropanol leaves 3.3 g of (—)-norephedrine hydrochloride.

Yield 74% of the theoretical;
m.p. 166—171°C.
$[\alpha]_D^{20}$ (in water, 5%): —32.3°.

Example 11
(+)-Phenylisopropylamine

40 g of (±)phenylisopropylamine and 36.9 g of (+)-ψ-NEMA are stirred for 10 hours in 190 ml of acetone. After standing for 15 hours at 20°C, the (+)-phenyl isopropylamine salt of the (+)-ψ-NEMA which has crystallised out is filtered off under suction.

Yield: 52.5 g=92.2% of the theoretical.
M.p. 150°C.
$[\alpha]_D^{20}$ (2.5% in ethanol): —48.0°.

50 g of this salt are stirred for 30 minutes with 30 ml of water and 11.7 ml of concentrated hydrochloric acid. The (+)-ψ-NEMA precipitated is filtered off under suction and dried *in vacuo* 35 g=95.5% of the theoretical). The aqueous filtrate is concentrated *in vacuo*, heavily alkalised with sodium hydroxide solution and the optically active amine separated off by extraction by shaking (five times) with chloroform. After the chloroform has been distilled off, the residue is dissolved in dry ether and the (+)-phenylisopropylamine is precipitated with isopropanolic hydrochloric acid. After standing for 2 to 3 days in a refrigerator, the hydrochloride is filtered off under the suction.

Yield: 17.2 g=76.2% of the theoretical;
m.p. of the hydrochloride: 149—151°C.
$[\alpha]_D^{20}$ (5% in water): +24.2° (hydrochloride).

Example 12
(+)-and (—)-α-phenylethylamine

100 g of racemic α-phenylethylamine and 102.8 g of (—)-ψ-NEMA are stirred for 7 hours at 20°C in 1 litre of acetone. After standing overnight, the product is filtered off under suction and recrystallised from ethanol.

Yield: 113.9 g of salt=74.5% of the theoretical.
M.p. 149—151°C.
$[\alpha]_D^{20}$ (2.5% in ethanol): +52.81°.

63.3 g of this salt are stirred for 20 minutes with 390 ml of water and 14.5 ml of concentrated hydrochloric acid and, after standing for a few hours at 10°C, the (—)-ψ-NEMA is filtered off under suction (43 g=98% of the theoretical).

The aqueous filtrate is heavily concentrated, 50 ml of 32% sodium hydroxide solution are added and the product extracted by shaking four times with ether. The combined ether extracts are dried with KOH, the ether is distilled off and the liquid residue is distilled at 12 mm Hg. The (+)-α-phenylethylamine is obtained in a yield of 19.9 g (=93.2% of the theoretical); m.p. 68—70°C.

$[\alpha]_D^{20}$ (5% in benzene): +40.9°.

To produce the (—)-α-phenylethylamine, the acetone filtrate from precipitation of the salt may be concentrated by evaporation and the residue distilled. The levorotatory amine is obtained in a yield of 88%. The specific rotation lies between 31° and 35°.

Optically highly pure (—)-α-phenylethylamine $[\alpha]_D^{20}$: —40° may be obtained by reacting the (±)-base with (+)-ψ-NEMA. The quantitative ratios, test conditions and yields are the same as in the above-mentioned production of the (—)-α-phenylethylamine.

Example 13

(+)- and (—)-p-hydroxy norephedrine

A mixture of 100 g of (±)-p-hydroxy norephedrine, 74.5 g of (+)-ψ-NEMA and 1.05 litres of acetone is stirred for 20 hours at 20 to 23°C and then left standing for 48 hours. The product is filtered off under suction and dried *in vucuo* at 60°C.

Yield 86.6 g=69.7% of the theoretical.
M.p. 98—104°C.
$[\alpha]_D^{20}$ (5% in ethanol): —62.5°.

80 g of this (+)-ψ-NEMA-salt are stirred with 96 ml of 2N NaOH for about 1 hour at room temperature. After standing overnight in a refrigerator, the product is filtered off under suction, washed with a little water and dried *in vacuo* at 40°C.

Yield: 23.7 g= 73.8% of the theoretical.

For further purification, the (—)-p-hydroxy norephedrine thus obtained may be recrystallised from isopropanol. M.p. 164—167°C. $[\alpha]_D^{20}$ (3.5% in 1N HCl): —40.94°.

The (+)-p-hydroxy norephedrine may be obtained from the acetone mother liquor by adding approximately 70 g of (—)-ψ-NEMA and standing for several days (approximately 3 days), the norephedrine compound precipitating in the form of the (—)-ψ-NEMA-salt. This salt may be decomposed in the usual way.

If (±)-p-hydroxy norephedrine is reacted with (—)-ψ-NEMA as described above, the pure (+)-form is directly obtained.

Example 14

(+)- and (—)-p-hydroxy norephedrine:

A mixture of 100 g of (±)-p-hydroxy norephedrine, 149 g of (—)-NEMA and 1.25 litres of absolute ethyl alcohol is stirred for 8 hours at 20°C and left standing for another 16 hours. The (—)-NEMA salt of the (—)-p-hydroxy norephedrine which crystallises out is filtered off under suction and thoroughly boiled with 550 ml of isopropanol for purification. After cooling, the product is filtered under suction and dried *in vacuo* at 60°C.

Yield: 94.3 g=75.7% of the theoretical.
M.p.: 163—165°C.
$[\alpha]_D^{20}$ (1% in absolute ethanol): +4.1°.

Recovery of the (—)-base:

The free base is obtained from the salt in accordance with Example 13.

Yield: 72.0%.
M.p.: 162—166°C.
$[\alpha]_D^{20}$ (2% in absolute ethanol): —17.5°
$[\alpha]_D^{20}$ (3.5% in 1N HCl): —40.7°.

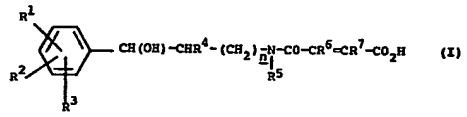
Recovery of the (+)-base:

The ethanolic filtrate from the racemate-splitting reaction is concentrated by evaporation *in vacuo* and the residue recrystallised from isopropanol. 127.5 g of crude (—)-NEMA-salt of (+)-p-hydroxy norephedrine are obtained. The (+)-base is precipitated therefrom by stirring with 152 ml of 2N NaOH, followed by standing for 12 hours in a refrigerator. The product is filtered off under suction and recrystallised from isopropanol.

Yield: 60.4%.
M.p.: 163—166°C.
$[\alpha]_D^{20}$ (2% in absolute ethanol): +17.35°.

Claims

1. Semi-amides of unsaturated aliphatic dicarboxylic acids corresponding to the general formula (I)



(I)

in which R^1, R^2 and R^3 which may the same or different, each represent hydrogen, a halogen atom, a hydroxy group, a methyl group or a methoxy group or two of these radicals taken together represent a methylene dioxy group, R^4 is hydrogen or a methyl group, the radicals R^5, R^6 and R^7 independently of one another each represent hydrogen or a C_1—C_4-alkyl group and n=0 or 1, and their salts, excluding N-[2-(3-hydroxyphenyl)-2-hydroxyethyl]-maleic acid monoamide in the case of the free acids.

2. Semi-amides as claimed in claim 1, in which R^3, R^5, R^6 and R^7 represent hydrogen, R^4 is a methyl group, R^1 represents hydrogen and R^2 is a hydroxy group, or both the radicals R^1 and R^2 represent hydroxy groups and their salts.

3. Salts of the semi-amides claimed in claim 2, with racemic or optically active β-phenylethylamine which may also contain a hydroxy group in the β-position, a methyl group in

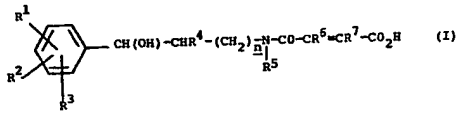
the α-position and one or two hydroxy groups on the phenyl ring.

4. Salts of semi-amides as claimed in claim 3, wherein the hydroxy groups in the phenyl ring of the β-phenylethylamine are in the 4-position and/or 2-position and/or 3,5-position.

5. The compounds of formula (I) as defined in claim 1 and their salts hereinbefore described in Examples 1 to 4.

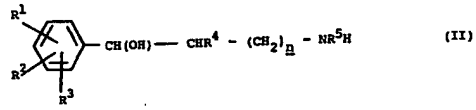
6. The compounds of formula (I) as defined in claim 1 and their salts hereinbefore described in Examples 5 and 6.

7. A process for the production of semi-amides of unsaturated aliphatic dicarboxylic acids corresponding to the general formula (I)



(I)

in which R^1, R^2 and R^3 which may be the same or different, each represent hydrogen, a halogen atom, a hydroxy group, a methyl group or a methoxy group or two of these radicals taken together represent a methylene dioxy group, R^4 is hydrogen or a methyl group, the radicals R^5, R^6 and R^7 independently of one another each represent hydrogen or C_1—C_4-alkyl groups and n=0 or 1, and their salts, excluding N-[2-(3-hydroxyphenyl)-2-hydroxyethyl]-maleic acid monoamide in the case of the free acids, which comprises reacting a compound corresponding to the formula (II)



(II)

with a compound corresponding to the formula (III)

$$X—CO—CR^6=CR^7—CO_2H \qquad (III)$$

in which formulae, the radicals R^1 to R^7 are as defined above and X is a halogen atom, a hydroxy group, a C_1—C_6-alkoxy group, a cyanomethoxy radical, a carboxymethoxy radical or an aryloxy group, or X forms a 5-membered acid anhydride ring with the free carboxy group.

8. A process as claimed in claim 7 in which any hydroxy groups present in the compounds of formula (II) or (III) and/or the carboxy group in the compound of formula (III) are protected.

9. A process as claimed in claim 7 or 8, wherein the compound obtained is converted into a salt by reaction with an amine or a basic metal compound.

10. A process as claimed in any of claims 7 to 9 for the production of semi-amides corresponding to formula (I), in which R^3, R^5, R^6 and R^7 represent hydrogen, R^4 is a methyl group, R^1 represents hydrogen and R^2 represents a hydroxy group or both R^1 and R^2 represent hydroxy groups, and their salts.

11. A process as claimed in any of claims 7 to 10 for the production of salts as claimed in claim 3 or 4 wherein a semi-amide as claimed in claim 2 is reacted with a racemic or optically active β-phenylethyl amine which may also contain a hydroxy group in the β-position, a methyl group in the α-position and one or two hydroxy groups in the phenyl ring.

12. A process as claimed in claim 7 substantially as described with particular reference to any of Examples 1 to 4.

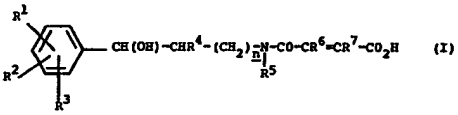
13. A process as claimed in claim 7 substantially as described with particular reference to either of Examples 5 or 6.

14. Compounds of formula (I) as defined in claim 1 or their salts when produced by a process as claimed in any of claims 7 to 13.

15. A pharmaceutical composition comprising at least one compound as claimed in any of claims 1 to 6 or 14 together with at least one pharmaceutically acceptable carrier or diluent.

16. A process for the production of a pharmaceutical composition wherein at least one compound as claimed in any of claims 1 to 6 or 14 is processed to form a pharmaceutical composition or is brought into a pharmaceutically useable form with one or more standard pharmaceutical excipients or diluents or other physiologically acceptable additives.

17. A process for the production of an optically active base which comprises reacting a racemic base with an optically active semi-amide of an unsaturated aliphatic dicarboxylic acid corresponding to the general formula (I)

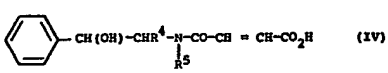


(I)

in which R^1, R^2 and R^3 which may be the same or different, each represent hydrogen, a halogen atom, a hydroxy group, a methyl group or a methoxy group or two of these radicals taken together represent a methylene dioxy group, R^4 is hydrogen or a methyl group, the radicals R^5, R^6 and R^7 independently of one another each represent hydrogen or a C_1—C_4-alkyl group and n=0 or 1.

18. A process as claimed in claim 17, wherein after fractionation at least one optically uniform salt fraction is split up into the corresponding optically active base and the semi-amide used.

19. A process as claimed in claim 17 or 18, wherein the reaction is carried out with a semi-amide corresponding to the general formula (IV)



(IV)

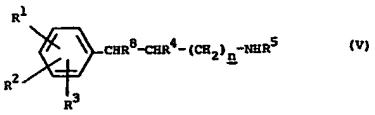
in which R^4 is hydrogen or a methyl group and R^5 is hydrogen or a C_1—C_4-alkyl group.

20. A process as claimed in claim 19, wherein in formula (IV) R^4 and R^5 are both hydrogen.

21. A process as claimed in claim 19, wherein in formula (IV) R^4 is a methyl group and R^5 is hydrogen.

22. A process as claimed in claim 19, wherein the maleic acid semi-amide of (+)-pseudonorephedrine or of (−)-pseudonorephedrine is used.

23. A process as claimed in any of claims 17 to 22 wherein the racemic base used is an amine corresponding to the general formula (V)



(V)

in which R^1, R^2 and R^3, which may be the same or different, each represent hydrogen, a halogen atom, a hydroxy group, a methyl group or a methoxy group or two of these radicals taken together represent a methylene dioxy group, R^4 is hydrogen or a methyl group, R^5 is hydrogen or a C_1—C_4-alkyl group, R^8 is hydrogen or a hydroxy group and n=0 or 1.

24. A process as claimed in claim 23, wherein a racemic amine of formula (V) is used in which R^1, R^2, R^3 and R^5 each represent hydrogen, R^8 is hydrogen or a hydroxy group, R^4 is a methyl group and n=0.

25. A process as claimed in claim 23, wherein a racemic amine of formula (V) is used in which R^1, R^2, R^3 and R^5 each represent hydrogen, R^8 is a hydroxy group, R^4 is hydrogen or a methyl group and n=0.

26. A process for the production of an optically active base substantially as described with particular reference to any of the Examples 9 to 13.

27. A process for the production of the optically active base substantially as described with particular reference to Example 14.

28. An optically active base when produced by a process as claimed in any one of claims 17 to 27.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1979. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.